Clinical Features and Epidemiology of Melioidosis Pneumonia: Results From a 21-Year Study and Review of the Literature

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Background. Melioidosis is an important cause of community-acquired sepsis in Southeast Asia and northern Australia, and pneumonia is the most common presentation. Clinical manifestations range from acute fulminant sepsis to chronic infection mimicking tuberculosis. Pneumonia may be the primary presenting feature, or it can develop secondary to initial disease at a distant focus.

Methods. A prospective database of all melioidosis patients at Royal Darwin Hospital (Australia) between 1989 and 2010 was reviewed.

Results. Of 624 patients with culture-confirmed melioidosis, 319 (51%) presented with pneumonia as the primary diagnosis. Acute/subacute presentations accounted for the majority of primary pneumonia cases (91%); chronic disease was seen less commonly (9%). Secondary pneumonia developed in 20% of patients with other primary melioidosis presentations and was particularly common in those with positive blood cultures. Risk factors for presentation with primary pneumonia (compared with other primary presentations) were rheumatic heart disease or congestive cardiac failure, chronic obstructive pulmonary disease, smoking, and diabetes mellitus, with $P < .05$ for these conditions in a multivariate logistic regression model. Patients presenting with pneumonia more frequently developed septic shock (33% vs 10%; $P < .001$) and died (20% vs 8%; $P < .001$) compared with patients with other primary presentations. Multilobar disease occurred in 28% of primary pneumonia patients and was associated with greater mortality (32%) than in those with single-lobe disease (14%; $P < .001$).

Conclusions. Melioidosis pneumonia is often a rapidly progressive illness with high mortality, particularly among those with multilobar disease. Risk factors have been identified, and early diagnosis and treatment should be priorities.

Pneumonia is the most common presenting feature of melioidosis, the disease caused by infection with *Burkholderia pseudomallei* [1, 2]. This environmental bacterium is found in soil and water in tropical regions. The majority of reported cases occur in Southeast Asia and northern Australia; however, the known area of endemicity is expanding and extends to other locations around the globe, predominantly but not exclusively between 20° North and 20° South [3].

It is likely that the vast majority of *B. pseudomallei* exposure occurs during the monsoonal wet season [4]. Percutaneous inoculation and inhalation are considered the major routes of acquisition of *B. pseudomallei*, although the relative contribution of each is unknown. Seroprevalence studies indicate that the majority of people exposed to *B. pseudomallei* are asymptomatic [5–7]. *B. pseudomallei* can remain latent for many years and then reactivate; however, most melioidosis cases are thought to occur soon after exposure [8]. Risk factors for developing clinical melioidosis have previously been well defined; comorbidities that lead to impaired immunological response and behavioral factors

that increase exposure to *B. pseudomallei* are important [4, 9, 10]. Risk factors specific for melioidosis pneumonia, however, have not been extensively examined.

Melioidosis pneumonia is a diverse illness that can range from acute, fulminant sepsis with multifocal lung infiltrates to chronic infection that mimics tuberculosis both clinically and radiologically [2]. Melioidosis pneumonia can be the primary presenting feature, can develop secondary to initial illness at a distant site, and can develop in patients with bacteremia without an initial evident focus [1]. The gold standard for diagnosis is culture and isolation of *B. pseudomallei* from patient samples. Rapid diagnostic tests have lacked sensitivity and/or specificity [11]. *B. pseudomallei* exhibits resistance to many antibiotics used in the empirical treatment of community-acquired pneumonia, necessitating the inclusion of broader-spectrum antibiotics in empirical treatment guidelines in endemic areas [12].

The objectives of this study were to describe the clinical features of melioidosis pneumonia, including the location and extent of pulmonary involvement, and to identify risk factors and prognostic markers of melioidosis pneumonia in the "Top End" of the Northern Territory, Australia.

METHODS

A prospective database was reviewed of all culture-confirmed melioidosis patients in the Top End of the Northern Territory, Australia, between October 1989 and August 2010. Data collection and storage methods and definitions of clinical parameters have been described previously [4]. Pneumonia was diagnosed on the basis of clinical symptoms and signs (fever, cough, shortness of breath, and/or pleuritic chest pain) with radiologic evidence of infection or by autopsy. Acute/subacute melioidosis was diagnosed if symptoms had been present <2 months; chronic melioidosis was diagnosed if symptoms at presentation had been present ≥2 months. Primary pneumonia was diagnosed when there were clinical and radiologic features of pneumonia present within 48 hours of admission and there was no other initial clinical focus evident. Secondary pneumonia was diagnosed when respiratory symptoms and pulmonary infiltrates developed >48 hours after admission in patients with an initial nonpulmonary presentation. Reactivation from a potential latent focus was considered possible in patients with evidence of *B. pseudomallei* exposure prior to presentation; this included indirect hemagglutination (IHA) titer >1:40 and/or preexisting radiologic evidence of a pulmonary nodule. The wet season was defined as the period from November 1 to April 30. Patients were treated according to Australian guidelines that recommend at least 2 weeks of ceftazidime or a carbapenem antibiotic, often combined with trimethoprim-sulfamethoxazole (TMP-SMX), followed by at least 3 months of TMP-SMX monotherapy [13]. Comparisons of proportions were made using the χ^2 test with

the null hypothesis rejected for $P < .05$. A logistic regression model comparing differences in epidemiologic and clinical features between patients with primary melioidosis pneumonia and those with other presentations was constructed to examine independent risk factors. This was performed by selection of variables that were associated with the outcome measure in a univariate analysis where $P < .2$ and backwards selection until remaining factors were associated with the outcome with $P < .05$. Statistical analysis was performed using Stata/IC 10 software. This study was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Families and the Menzies School of Health Research (HREC 02/38).

RESULTS

There were 624 cases of culture-confirmed melioidosis between 1989 and 2010. The median age was 49.5 years (range, 8 months–91 years); 430 patients (69%) were male, 326 (52%) were Indigenous Australians, and 233 (37%) lived in remote locations. There were 319 cases of primary pneumonia, accounting for 51% of presentations. Primary pneumonia accounted for a greater proportion of cases in the wet season (281 cases, 56%) compared with the dry season (38 cases, 31%; $P < .001$). Of the patients with primary nonpulmonary presentations, 59 (19%) developed secondary pneumonia during the course of their illness.

Chest radiographic results were available for 305 of 319 patients with primary pneumonia. Of the 14 patients without chest radiographic results, 9 patients had infective changes on chest radiography, but the location within the lungs was not known; 3 patients were deceased on arrival to hospital, and chest radiography was not performed (pneumonia diagnosed at autopsy); 1 patient was evacuated interstate before chest radiography was done; and 1 patient had lung cancer that obscured infective changes.

Six additional patients presented with mild respiratory illness and did not have changes consistent with pulmonary infection on chest radiography; 5 of 6 patients had *B. pseudomallei* isolated from sputum and/or throat swabs, and the remaining patient had *B. pseudomallei* isolated from an unrecorded sample type. All 6 patients had negative blood cultures and survived their illness. These 6 patients were excluded from subsequent analysis.

The majority of primary pneumonia cases were acute/subacute (291 cases, 91%); chronic disease (28 cases, 9%) was seen less commonly. Reactivation of infection from a latent focus was considered possible in 13 (4%) primary pneumonia patients. Of these, 12 had acute/subacute presentations, and 1 had a chronic presentation. Acute/subacute infection was associated with bacteremia, septic shock, and death (Table 1). While upper-lobe involvement was common in both acute/subacute

Table 1. Features of Acute/Subacute and Chronic Primary Pneumonia

	Acute/Subacute Primary Pneumonia (n = 291)	Chronic Primary Pneumonia (n = 28)	P Value
Bacteremia	196[a] (69%)	2 (7%)	<.001
Septic shock	105 (36%)	0	<.001
Death	63 (22%)	1 (4%)	.023
Upper-lobe involvement	128[b] (46%)	17 (61%)	.143
Lower-lobe involvement	151[b] (55%)	8 (29%)	.009
Multilobar involvement	82[b] (30%)	3 (11%)	.034

[a] Blood cultures not done in 7 cases.

[b] Chest radiographic results unavailable in 14 cases.

and chronic pneumonia, lower-lobe involvement and multi-lobar involvement were less common in patients with chronic pneumonia in comparison to those with acute/subacute pneumonia (Table 1). Figures 1-4 show examples of chest radiographic and computed tomographic findings.

Secondary pneumonia occurred in 48 of 154 (31%) patients with extrapulmonary presentations and positive blood cultures but in only 11 of 143 (8%) patients with negative blood cultures (P < .001). Despite high rates of bacteremia and multilobar disease, patients with secondary pneumonia were considerably less likely than those with primary bacteremic pneumonia to develop septic shock or die (Table 2). Lower-lobe and multilobar disease predominated among secondary pneumonia patients; upper-lobe disease was less common than among primary pneumonia patients (Table 2).

Univariate and multivariate analyses of risk factors for primary melioidosis pneumonia (compared with other primary presentations) are presented in Table 3. In a multivariate logistic regression model, comorbidities that were associated with primary pneumonia included rheumatic heart disease or congestive cardiac failure (RHD/CCF), chronic obstructive pulmonary disease (COPD), current smoking, and diabetes mellitus. Hazardous alcohol use was significant in the univariate analysis only and appeared to be collinear with smoking.

Compared with melioidosis patients with other primary presentations, patients with pneumonia more frequently had bacteremia, developed septic shock, and died from their illness (Table 4). Sixty-four of 319 (20%) patients with primary pneumonia died. Of these deaths, 63 occurred during the initial hospital admission, and the time from admission to death ranged from 0 to 111 days (median, 3 days). Six patients were dead on arrival at hospital, 3 died on the day of admission, and 8 died the day after admission. In contrast, only 25 of 299 (8%; P < .001) patients with other primary presentations died. Multilobar involvement was present in 85 of 305 (28%) patients with primary pneumonia who had chest radiographic results
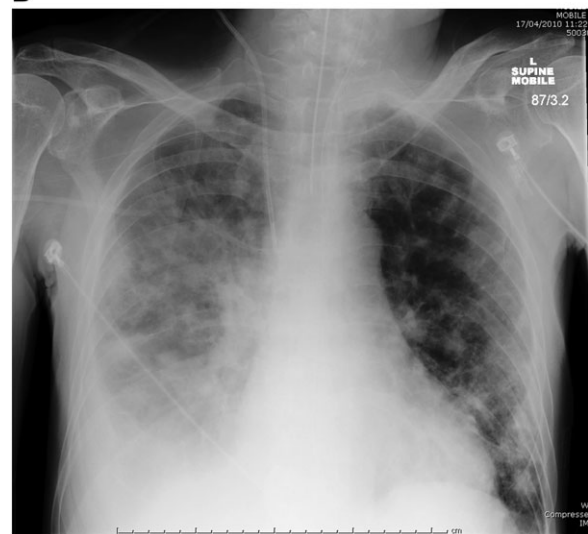

Figure 1. Two fatal cases of septicemic melioidosis pneumonia.

available and was associated with increased severity and higher mortality (Table 5).
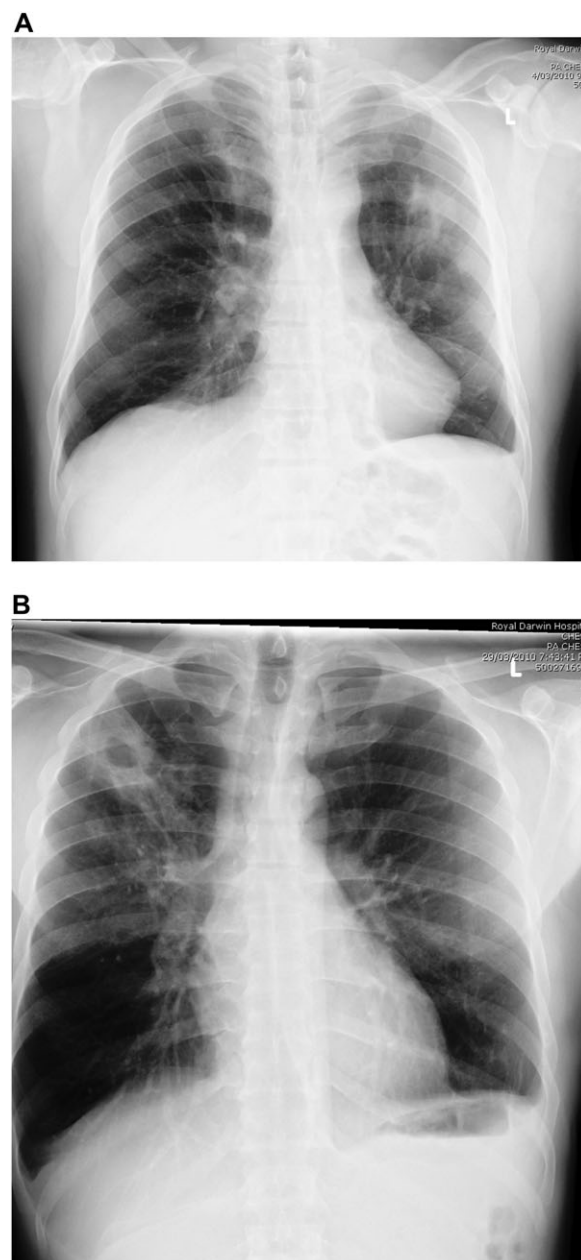
DISCUSSION

The clinical features and severity of pulmonary melioidosis exist in a spectrum ranging from mild respiratory illness, to chronic infection similar to tuberculosis, to acute pneumonia that rapidly progresses to septic shock and death. Acute/subacute primary pneumonia accounts for the majority of cases. Patients with bacteremic melioidosis pneumonia can present severely unwell with fever and prostration, sometimes with few clinical features to suggest a focus of infection but with chest radiography revealing abnormalities consistent with bacteremic pneumonia, typically multiple nodular opacities or multiple
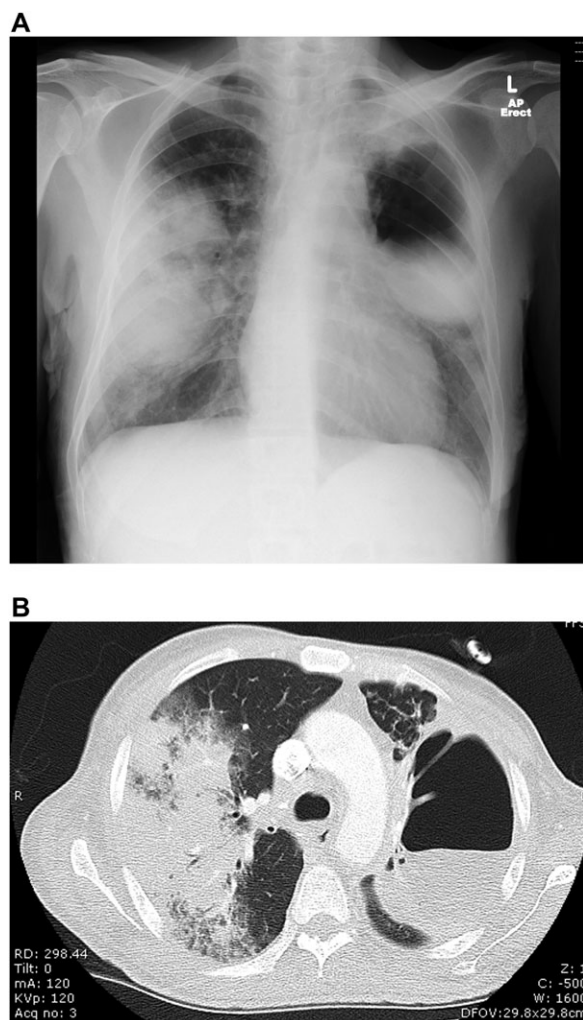
Figure 2. Chest radiograph (*A*) and computed tomographic scan (*B*) of bilateral melioidosis pneumonia with large left lung abscess.

Figure 3. Two cases of melioidosis mimicking tuberculosis.

patches of alveolar infiltration [10, 14, 15]. These cases often progress rapidly with coalescence of lesions, development of new lesions, and cavitation [16]. Other patients with acute/subacute melioidosis pneumonia present with more prominent respiratory symptoms and signs and may have more focal consolidation on chest radiography [10, 16, 17]. Clinical progression of acute melioidosis pneumonia is often rapid, and septic shock and death are common outcomes [14, 15, 18, 19].

The radiologic features and outcomes of acute/subacute melioidosis pneumonia reported here differ from findings in Southeast Asia. Compared with other reported case series, multilobar disease and death were less common than in northeast Thailand and Singapore, and upper-lobe involvement was more common than reported in Singapore but less common than in Thailand [16, 18]. The relative contributions of regional differences in strain virulence, possible differences in the mode and magnitude of infecting inoculums, and differences in access

to medical care and timeliness and availability of antibiotics effective against *B. pseudomallei* are not known. We have previously speculated that changes in severity of disease may represent a shift in the mode of acquisition from percutaneous exposure to inhalation, particularly during severe weather events [20]. This is also likely to be reflected in the higher mortality of primary pneumonia compared with infection confined to other sites and compared with secondary pneumonia presenting subsequent to infection at other sites.

At the other end of the spectrum is chronic melioidosis pneumonia. This typically presents with symptoms similar to
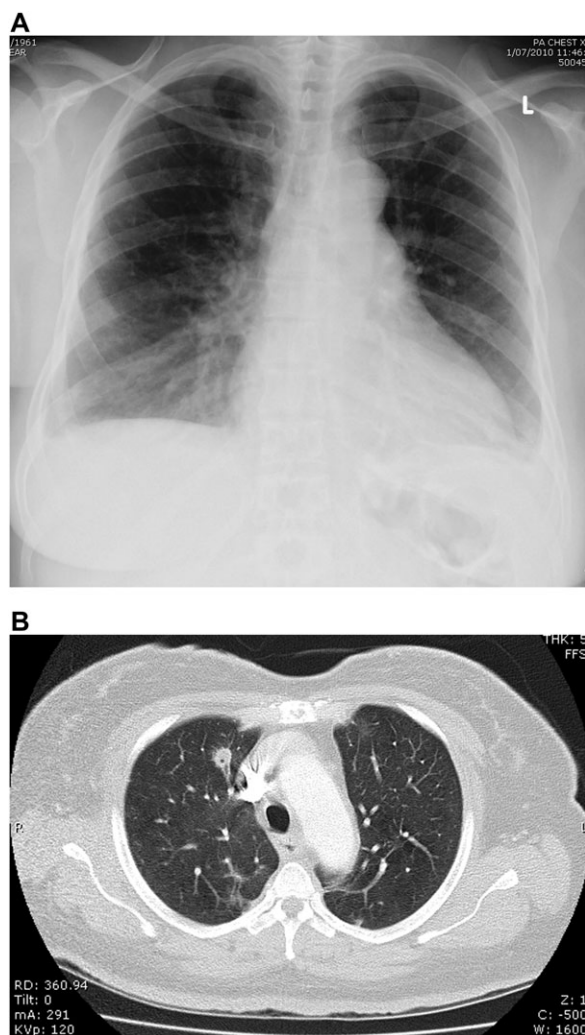
Figure 4. Melioidosis pneumonia not evident on a chest radiograph (*A*) and with small right upper-lobe cavity on computed tomographic scan (*B*).

In chronic pulmonary melioidosis, the upper lobes are often affected and have previously been reported to be involved in up to 95% of cases [22]. Common findings include cavities, nodules, and fibroreticular and patchy alveolar infiltrates [16, 17, 22]. Hilar lymphadenopathy occurs in a minority of cases. Single or multiple lung abscesses and pleural effusion/ empyema can occur in both acute and chronic forms of the disease [16, 17]. Although chronic melioidosis pneumonia affects the upper lobes in almost two-thirds of cases, this proportion is lower than that described for tuberculosis, in which upper-lobe involvement has been described in 86% of cases [23]. However, the proportion of tuberculosis patients with lower-lobe or diffuse opacities increases in the setting of human immunodeficiency virus (HIV) coinfection and low CD4 cell count [24].

A minority of patients presented with a mild respiratory illness and did not have chest radiographic changes, but *B. pseudomallei* was cultured from sputum or throat swabs. These patients were not severely unwell, and all had negative blood cultures. It is likely that this represents respiratory tract melioidosis at the milder end of the spectrum rather than incidental detection of colonizing *B. pseudomallei*. Positive sputum culture among melioidosis patients without radiologic changes was previously reported in a Thai series in which 40% of melioidosis patients with a normal chest radiograph had *B. pseudomallei* isolated from sputum [25]. Lung colonization is rare and has mainly been associated with cystic fibrosis or severe bronchiectasis [4, 26]. Furthermore, *B. pseudomallei* isolated from throat swab was found to be 100% specific for clinical melioidosis in a large Thai study that included 3524 healthy subjects as controls [27].

A small number of patients with primary melioidosis pneumonia had evidence of previous exposure to *B. pseudomallei* in the form of positive IHA or preexisting pulmonary opacities, which may indicate latency analogous to tuberculosis. This is consistent with reports of disease with prolonged incubation periods of up to 62 years [28]. Nevertheless, latency with subsequent activation accounts for only a small minority of cases

tuberculosis, including fever, night sweats, weight loss, and sometimes hemoptysis [2]. The radiologic features can be difficult to distinguish, and patients with chronic melioidosis may be initially misdiagnosed as having tuberculosis [21, 22].

Table 2. Severity and Chest Radiographic Findings of Primary and Secondary Pneumonia

	Primary Pneumonia, Blood Culture Positive[a] (n = 198)	Primary Pneumonia, Blood Culture Negative[a] (n = 114)	Secondary Pneumonia (n = 59)	P Value
Septic shock	94 (47%)	4 (4%)	9[b] (16%)	<.001
Death	53 (27%)	4 (4%)	5 (8%)	<.001
Upper-lobe involvement	86[c] (45%)	55[d] (50%)	17[b] (29%)	.031
Lower-lobe involvement	116[c] (60%)	41[d] (38%)	37[b] (64%)	<.001
Multilobar involvement	64[c] (33%)	19[d] (17%)	22[b] (38%)	.004

[a] Blood cultures not done in 7 primary pneumonia patients.

[b] Septic shock and chest radiographic data unavailable in 1 case.

[c] Chest radiographic results unavailable in 6 cases.

[d] Chest radiographic results unavailable in 5 cases.

Table 3. Risk Factors for Primary Pneumonia Compared With Other Primary Presentations

	Primary Pneumonia (n = 319)	Other Primary Presentations (n = 299)	Univariate Analysis		Multivariate Analysis	
			OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Age, median (range)	51 y (8 m–91 y)	47 y (9 m–85 y)	...	.001	...	...
Female sex	112 (35%)	78 (26%)	1.53 (1.08–2.17)	.015	1.60 (1.08–2.38)	.019
Indigenous ethnicity	177 (55%)	144 (48%)	1.34 (.977–1.84)	.069	...	...
Urban location	209 (66%)	179 (60%)	0.785 (.566–1.09)	.146	...	...
Wet-season presentation	281 (88%)	217 (73%)	2.79 (1.81–4.30)	<.001	2.62 (1.64–4.18)	<.001
RHD/CCF	38 (12%)	11 (4%)	3.54 (1.76–7.13)	<.001	2.91 (1.37–6.15)	.005
COPD	114 (36%)	49 (16%)	2.84 (1.92–4.20)	<.001	2.51 (1.62–3.91)	<.001
Smoking	211[a] (68%)	137[a] (48%)	2.33 (1.65–3.27)	<.001	1.98 (1.36–2.91)	<.001
Diabetes mellitus	150 (47%)	101 (34%)	1.74 (1.25–2.42)	.001	1.45 (1.01–2.10)	.046
Hazardous alcohol use	146 (46%)	101 (34%)	1.65 (1.19–2.30)	.002	...	...
Kava use	6[b] (2%)	21[b] (7%)	0.262 (.103–.663)	.002	0.286 (.101–0.805)	.018
Malignancy	14 (4%)	25 (8%)	0.503 (.256–.990)	.042	0.479 (.229–1.00)	.051
Chronic renal disease	36 (11%)	36 (12%)	0.929 (.568–1.52)	.770	...	...

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio; RHD/CCF, rheumatic heart disease/congestive cardiac failure.

[a] Smoking data unavailable for 10 patients with pneumonia and for 14 patients with other presentations.

[b] Kava data unavailable for 17 patients with pneumonia and for 7 patients with other primary presentations.

[4]. The tests available to diagnose latency are imperfect, and the risk factors and mechanisms for latency being established after infection with *B. pseudomallei* and the sites where latency occurs are unknown [29]. The factors that lead to impaired control of latent infection and precipitate the activation are as yet undefined but are likely to include the classical risk factors for melioidosis.

Host factors are likely to be important in determining organ involvement in melioidosis [30]. In comparing patients with primary pneumonia with those with other primary presentations, RHD/CCF, COPD, smoking, and diabetes mellitus were identified as independent risk factors for primary melioidosis pneumonia. Hazardous alcohol use was significant on univariate analysis only. RHD/CCF, COPD, and smoking may predispose to pulmonary infection via local immune dysfunction [4, 31] and have previously been identified as independent risk factors for community-acquired pneumonia in several large population-based case-control studies [32, 33]. Previous studies

from Thailand have found a similar proportion of patients with diabetes (44%–47%) [17] but also identified renal failure as a potential risk factor [25]. However, although renal failure is common in our patient population [34], its etiology differs from that in Thailand, where it is predominantly due to renal tubular acidosis and associated renal calculi [25]. Only 2 patients with melioidosis pneumonia in our series had HIV coinfection. In contrast to tuberculosis, infection with HIV has not been identified as a risk factor for developing melioidosis, nor does it appear to alter the clinical manifestations or progression of melioidosis [35]. Kava use and male sex were identified as risk factors for extrapulmonary disease, which is consistent with the previously identified association between kava use and melioidosis prostatic abscess [36]. The reasons for this association are unclear.

There were several limitations to this study. We have described the observed clinical features in our cohort of patients, but we can only speculate on the reasons for the observed

Table 4. Severity of Primary Pneumonia Compared With Other Primary Presentations

	Primary Pneumonia (n = 319)	Other Primary Presentation (n = 299)	P Value
Bacteremia	198[a] (63%)	154[a] (52%)	.004
Septic shock	105 (33%)	30[b] (10%)	<.001
Death	64 (20%)	25 (8%)	<.001

[a] Blood cultures not done in 7 patients with pneumonia and in 2 patients with other primary presentations.

[b] Septic shock information unavailable for 2 patients.

Table 5. Severity of Multilobar Disease Compared to Single-Lobe Disease in Primary Pneumonia Patients With Chest Radiographic Results

	Multilobar Involvement (n = 85)	Single-Lobe Involvement (n = 220)	P Value
Bacteremia	64[a] (77%)	128[a] (59%)	.003
Septic shock	41 (48%)	56 (25%)	<.001
Death	26 (32%)	31 (14%)	.001

[a] Blood cultures not done in 2 patients with multilobar involvement and in 2 patients with single-lobe involvement.

differences in this observational study. Chest radiographic findings are probably not sensitive enough, when compared with other imaging modalities such as computed tomography, to define the extent of involvement; however, this was the only radiologic imaging performed for many patients. Finally, we are not able to comment on other radiologic findings such as the presence of effusions/empyema, cavitation, and mediastinal involvement, because we did not collect these data.

B. pseudomallei is an important cause of severe community-acquired pneumonia in endemic areas and should also be considered in returning travelers and immigrants from endemic areas. The clinical features of melioidosis pneumonia cannot be distinguished reliably from pneumonia caused by other pathogens. Confirmation of the diagnosis by culture and isolation of *B. pseudomallei* usually takes at least 2 days and often longer, and it is therefore important that empirical community-acquired pneumonia treatment guidelines used in melioidosis-endemic areas include antibiotics effective against *B. pseudomallei* [12].

Notes

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